REMARKS/ARGUMENTS

1. Amendments

Claims 1, 4-6, 9, 10,11-14, 16-34, 40-49 are in the application. Claims 45-49 have been withdrawn. Claim 5 has been amended to incorporate the recitation of dependent claim 6. Claim 6 has been canceled without prejudice to filing a continuation application directed to the canceled subject matter. No new matter is added by these amendments.

2. Rejection of Figure 9

Figure 9 stands rejected because the half-tone of the figure is allegedly too dark. Applicant hereby provides a new Figure 9. Withdrawal of this rejection is respectfully requested.

3. Rejection under 35 U.S.C. § 112, first paragraph. (Enablement)

Claims 1, 4-6, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for (1) isolated fusion molecule comprising hinge CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:1 fused to a full length myelin basic protein comprising SEQ ID NO:12 or a peptide from myelin basic protein consisting of SEQ ID NO:13, and (2) an isolated fusion molecule comprising hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:1 fused to human IgE constant region CH2-CH3-CH4 domains for inhibiting IgE mediated release of histamine, does not reasonably provide enablement for any fusion molecule as set forth in claims 1, 4-6, 9-14, 16-34 and 40-44.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic

myelin protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor

Applicant traverses the rejection for the following reasons.

The test for enablement entails an analysis of whether one skilled in the art is able to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification, and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "[l]imitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled.

The nature of the invention

The present invention concerns certain novel fusion molecules that are capable of cross-linking a native IgG inhibitory receptor with a native IgE receptor. The fusion molecules comprise a sequence comprising at least 85% identity to IgG heavy chain sequence linked to a polypeptide autoantigen sequence which comprises at least 90% identity to myelin basic protein and is capable of being specifically bound by an immunoglobin specific for myelin basic protein. The purpose of these molecules is to allow the myelin basic peptide to function as an immunogen while any fusion peptides that reacted with IgE loaded mast cells would not trigger an adverse reaction.

While the therapeutic strategy and the construct underlying the present invention is both novel and unobvious, the fusion molecules themselves have a relatively simple structure, and can be made and tested by standard techniques that were well known in the art at the time of making the present invention. Furthermore, at the time the present invention was made, there was a lot of information known in the art about the interaction of IgG inhibitory receptors and IgE receptors with antibody constant regions, which provides valuable information for the construction of the fusion molecules of the present invention. Accordingly, although unpredictability in the field of recombinant DNA technology is generally viewed as relatively high, the unpredictability in the particular field to which the present invention pertains is of lesser degree.

The level of ordinary skill in the art

It is well established that the level of skill in the art of recombinant DNA technology is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

The Office Action indicates that there is insufficient guidance as to the structure of the first polypeptide "comprising at least 85% identity" with IgG heavy chain constant region because the term "comprises" is allegedly open-ended. Without knowing the length of the first polypeptide, it is not clear how one of ordinary skill in the art can ascertain the sequence identity based on the total number of amino acids in the first polypeptide. Further, there is insufficient evidence as to which amino acids within the IgG heavy chain constant region can be substituted, deleted added etc.

With regard to the "second polypeptide" the Office Action states that there is insufficient guidance as to which "portion" of the amino acid sequence of myelin basic protein (MBP) is part of the fusion molecule without the amino acid sequence. Further there is inadequate guidance as to which amino acids are to be added, deleted, substituted etc, such that the MBP will be able to bind to any native IgE receptor through any third polypeptide sequence. Given the unlimited number of fusion molecules there is allegedly a lack of in vivo working examples demonstrating any fusion molecule is effective for treating autoimmune disease.

Further, the Office Action alleges that the specification discloses binding between second polypeptide and an IgE receptor occurs indirectly via specific IgE molecules (page 36, line 10) not any immunoglobulin as recited in claim 5. Applicant has amended claim 5 to recite an IgE immunoglobulin. Withdrawal of the rejection of claim 5 on this basis is requested.

The Examiner cites Stryer et al., that a protein is highly dependent on the over all structure of the protein itself. The Examiner cites Ngo et al., that amino acid positions within the protein that can tolerate change such as conservative substitutions which are critical to maintain the protein's structure/function will require guidance. The Examiner cites Mikayama et al., as teaching that the GIF protein differs from the MIF protein by a single amino acid residue and yet has a different function.

The specification provides adequate disclosure for the following reasons. Applicant points out that Claim 1 and all claims dependent on Claim 1 contain the functional limitation that the IgG domain has the ability to bind to the native IgG inhibitory receptor. The sequence of the IgG heavy chain domain was known in the art at the time of filing. Figure 1 provides the nucleotide sequence encoding the human IgG1 heavy chain constant region. Figure 2 provides the amino acid sequence. Page 26 of the specification provides numerous references which describe the sequences of immunoglobulin heavy chain constant regions, such as Ellison et al., Nucleic Acid Res. 10:4071-79 (1982). The Specification teaches which amino acids are necessary for IgG receptor binding (see page 35, lines 1 - 25) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15-25). Thus, use of the term “comprising” does not result in an infinite number of fusion

molecules with unpredictable activities as the Examiner contends, rather identification of fusion molecules that meet the limitation of the claims would be routine and would not require undue experimentation.

With regard to the second polypeptide, Applicant maintains that one of skill in the art would know which portion was required for binding to the third polypeptide which would bind to the IgE receptor. The sequence for MBP was known in the art prior to the date of Applicant's filing. Applicant provides a number of references in the specification at page 46 which provide the sequence for MBP, see for example Warren et al., Proc. Natl. Acad. Sci USA 92:11061-11065 (1995). The specification identifies the MBP epitope necessary for binding with the autoantibody as MBP83-99. Furthermore, the Examiner references Warren et al., (1995 abstract) as teaching that the administration of MBP75-95 resulted in significant autoantibodies, but the administration of MBP35-58 did not affect the anti-MBP level. Accordingly, one of ordinary skill in the art would certainly know which portion of the MBP protein is specifically bound by autoantibodies.

Furthermore, it is not necessary to provide the amino acid sequence in the specification where the sequence is known in the art. The United States Court of Appeal for the Federal Circuit held in *Capon v. Eshar* (418 F.3d 1349: 2005 (U.S. App); 76 USPQ (BNA) 1078) that:

> *[t]he chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specification do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.*

The Office Action states that with regard to the percentage sequence identity (claims 1 and 18-21), in addition to the lack of sequence for the first and second polypeptides in the fusion molecule mentioned above, there is insufficient guidance as to which amino acids within the full-length polypeptide can be modified and yet maintain its function. The Office action states that the term "comprising" expands the IgG heavy chain constant region to include the Fab region of the whole IgG. Without knowing the length of the first polypeptide, it is not clear how one of ordinary skill in the art could

determine the sequence identity that is based on the total number of amino acids in the first polypeptide.

Applicant notes that the term "IgG heavy chain constant region" is defined in the specification at pages 26 and 36. It does not include the Fab region. Accordingly the term "comprising 85% of the IgG heavy chain constant region" means that the first polypeptide must exhibit at least 85% identity with the IgG heavy chain constant region. There may of course be additional amino acid residues included in the fusion peptide. However, one of ordinary skill in the art would know whether the fusion molecule contained an amino acid sequence with 85% identity to the IgG heavy chain constant region. Applicant points out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4. - 13). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Also, one of ordinary skill in the art will recognize that the prior art provides numerous sources that describe IgG Fc sequences highly homologous to the Fc sequences of SEQ ID NO: 3 *(see,* the Specification at page 26, line 19 - page 27, line 6). Furthermore, Applicant asserts that one of ordinary skill in the art has a sufficiently high level of technical competence to experimentally identify novel Fc sequences having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using the NCBI BLAST sequence identity values or the hybridization methods provided in the Specification (see, page 23, line 16 to page 24, line 12). Alternatively, one of ordinary skill in the art can readily engineer novel Fc domains exhibiting at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using recombinant DNA/protein engineering techniques. Thus, detailed protocols for the construction of fusion molecules having at least 85% sequence identity with a known Ig constant domain in the Specification is not necessary in order for one of ordinary skill to practice the claimed invention without undue experimentation. Accordingly, the rejection under 35 U.S.C. § 112, paragraph 1 should be withdrawn

Similarly one of ordinary skill in the art, based on the disclosure in the specification could construct MBP amino acid sequences having at least 90% sequence identity with the known MBP protein.

Moreover, it is well-known in the art that many, if not most, polypeptides of the invention exhibiting at least 85% sequence identity with the constant domain sequence of SEQ ID NO: 3 will retain biological activity. This is because one of ordinary skill in the art is fully aware of amino acid substitutions that are either less likely or not likely to significantly affect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid). For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in J. U. Bowie, *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-10 (1990) (copy enclosed), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

In addition, amino acids in the fusion proteins of the present invention that are essential for function can be easily identified by methods well-known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (*see*, *e.g.*, Cunningham and Wells, *Science* 244:1081-85 (1989) (copy enclosed)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, for example, as taught in the routine assays provided in the specification.

The claims currently recite peptide sequences associated with biological activity. This biological activity with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, is believed to sufficiently define the claimed genus such that, one of ordinary skill in the art, at the effective date of the present application, would have known how to make and use the claimed peptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation," *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v A.B. Fortia* 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *M.P.E.P. 2164.01*

The Office Action cites Attwood et al., that protein function is context dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequence and the current structure prediction methods is

unreliable. The Office Action also cites Skolnick et al., that sequence based methods for function prediction are inadequate and knowing a proteins structure does not tell one its function.

The citation of these references is misplaced here. Applicant is not identifying a function associated with a protein based on sequence homology of the protein to known peptides. Applicant has described a chimeric protein comprising two known sequences with known function. Accordingly, withdrawal of this portion of the rejection is respectfully requested.

The Examiner reasons that fusion molecules "comprising" first and second polypeptide sequences are not enabled, as use of the term "comprising" expands the hinge of a human IgG1 constant region to include additional amino acids at either ends of the first polypeptide within the claimed fusion molecule. There is allegedly a lack of guidance as to which amino acids are to be included.

Applicant must respectfully disagree. The present application describes, by way of example, additional non-essential but advantageous amino acid sequences and other elements that find use with the first and second polypeptides of the fusion molecules of the invention. For example, the first and second polypeptide sequences of the fusion molecule can be joined using various linkers (such as those described in the Specification at page 56, lines 4-16). Also, the fusion molecules may contain posttranslational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation (see Specification page 21, lines 4 - 24). The Specification teaches that fusion polypeptide variants can be constructed that contain advantageous insertions of various amino acid sequences (page 21, line 25 to page 23, line 3), resulting in fusion molecules that have improved affinity for their respective IgG or IgE Fc receptors (Specification, page 34, line 24 to page 35, line 25). The fusion molecules of the invention can also comprise multiple copies of the IgG and autoantigens, as described in page 54, lines 18-21. Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification (page 63, line 32 to page 64, line 3) also find use with the fusion molecules of the invention.

As outlined above, the Specification provides sufficient guidance to make a variety of advantageous fusion molecules comprising first and second polypeptide sequences. Applicant submits that fusion molecules comprising first and second polypeptides are fully enabled in view of 1) guidance provided throughout the Specification[1] (as described above), 2) the routine nature of recombinant DNA engineering and the production of chimeric or variant polypeptides, as known in the art, and 3) the high level of technical competence of one of ordinary skill in the immunological, genetics and protein-chemistry arts. The routine nature of manipulation of DNA and protein molecules is well known, as evidenced by the publications cited in the Specification *(see,* especially, page 20, line 29 to page 21, line 24; page 64, lines 17 - 26). Detailed protocols for the construction of the fusion molecule variants described in the Specification is not necessary for one of ordinary skill to practice the claimed invention without undue experimentation.

The Examiner asserts that there is also insufficient guidance as to which "portion" of the IgG in the fusion molecule is effective. Applicant respectfully disagrees. Applicant points out that Claim 1 and all claims dependent on Claim 1, including claim 25, contain the functional limitation that the IgG domain has the ability to bind to the native IgG inhibitory receptor and that the myelin basic protein (MBP) is capable of specific binding by a third polypeptide to a native IgE receptor. The Specification teaches which amino acids are necessary for IgG receptor binding (see *e.g.* page 35, lines 1 - 25) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15-25). The specification defines the term "portion" on page 29, lines 21 - 30. The specification teaches which amino acids comprise the epitopes of MBP (page 29, lines 7 to 11 and page 46, Table 2) Thus, use of the term "portion" does not result in an infinite number of fusion molecules with unpredictable activities as the Examiner contends, and the identification of fusion molecules that meet the limitation of the claims is routine and does not require undue experimentation.

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[1] Applicant points out that the guidance provided in the Specification is found both in the Experimental Example as well as in the description of other preferred embodiments elsewhere in the Specification.

Applicant submits that use of the open-ended transitional phrase "comprising" is appropriate, that the term "portion" is appropriate and that the claims are enabled and commensurate in scope with the disclosure, and are allowable. The Examiner is respectfully requested to withdraw this rejection.

Lack of in vivo working examples

The Examiner indicates that there is a lack of *in vivo* working examples demonstrating that the fusion molecule is effective for treating multiple sclerosis. The Examiner relies on Blanas et al., Couzin et al. and Mackay et al[2]. The Examiner states that the fusion molecule may be inactivated before producing an effect; the fusion molecule may not reach its targeted area. The Examiner also cites McDevitt et al., as teaching that administration of epitopes of the GAD autoantigen to NOD mice result in the prompt onset of an immediate hypersensitivity and death of the animal.

The legal standard with respect to in vitro or animal model data providing pharmacological activity was set forth by the United States court of Appeals for the Federal Circuit in its opinion Cross v Iizuka 753 F. 2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985).

> *"We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vitro utility."*

Furthermore, M.P.E.P. 2107.03 (III) states that,

> *"[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."*

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[2] Applicant presumes that the Examiner intended to cite Davidson et al., (2001) New England J. of Med. 345(5) 340-350, Eds. MacKay & Rosen rather than MacKay et al.

Thus, the legal standard requires that *in vitro* or animal model data is be acceptable as a basis for enablement.

Blanas indicates that oral administration of ovalbumin autoantigen in mice was found to induce a cytotoxic T lymphocyte response that could lead to the onset of autoimmune diabetes. Blanas does not discuss the MBP peptide or multiple sclerosis. Applicant's construct comprises the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction. Blanas does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Accordingly, the findings of Blanas cannot be applied properly to the currently claimed invention.

Couzin et al. (2003) is an article reviewing various clinical tests for the treatment and prevention of type I diabetes. Couzin does not discuss the MBP peptide, use of a fusion polypeptide or multiple sclerosis. For the reasons set forth for Blanas, the findings of Couzin et al. cannot be applied properly to the currently claimed invention. Furthermore, the legal standard sufficient to establish enablement of a compound is *in vitro* or *in vivo* animal model tests. In any case, human clinical trials are not required.

Mackay et al., states that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. (page 346) First, MacKay does not indicate that the altered peptide ligands derived from MBP are functionally attached to the IgG heavy chain constant regions. The purpose of the IgG Fc regions is to prevent the hypersensitivity reaction seen with the peptides as taught by MacKay. Accordingly, MacKay does not teach that the claimed invention will not work. Furthermore, the legal standard sufficient to establish enablement of a compound is *in vitro* or *in vivo* animal model tests. In any case, human clinical trials are not required.

McDevitt, allegedly indicates that administration of GAD autoantigen epitopes in NOD mice was found to induce immediate hypersensitivity that could lead to death. Applicant's fusion molecules comprise the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction.

McDevitt does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Accordingly, the findings of McDevitt cannot be applied to the currently claimed invention. Indeed, use of an autoantigen fused to the IgG heavy chain constant region as proposed by Applicant would be the way to resolve the problem discussed by McDevitt.

Applicant previously enclosed later published papers which show that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals. Clearly such compounds are not inactivated as suggested by the Examiner. Clearly these types of fusion molecules can be successfully administered to animals[3].

Furthermore, the appearance of IgG or other antibodies against the MBP portion of the fusion molecule would not be a problem because the purpose of the molecule is to present the MBP as an "immunogen" while any reacted IgE loaded mast cells would be suppressed by the IgG Fc portion.

For the above reasons, Applicant asserts that the presently claimed invention is fully enabled under 35 U.S.C. § 112, first paragraph and respectfully requests that the Examiner withdraw this rejection.

4. Rejection under 35 U.S.C. § 112, first paragraph. (Written Description)

Written Description

Claims 1, 4-6, 9-14, 16--34 and 40-44 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking written description. Specifically, the Examiner alleges that there is insufficient written description in the Specification for the same fusion molecules that were rejected on the basis of lack of enablement (see above, and Office Action, pages 7-8).

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[3] Zhu et al., "A novel human immunoglobulin Fcγ-Fcε bifunctional fusion protein inhibits Fcε RI mediated degranulation". (2002) *Nature Medicine* vol. 8 (5) 518-521; Kepley et al. "FcεRI-FcγRII coaggregation inhibits IL-16 production from human langerhans-like dendritic cells" (2003) *clinical Immunology* vo. 108 p. 89-94

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor.

Applicant traverses the rejection for the following reasons.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention (e.g., *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 563, 19 USPQ 2d at 1116 and *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473, 45 USPQ 2d 1498 [Fed. Cir. 1998]). Applicant asserts that they have met this requirement. Applicant emphasizes that sufficient written description must be ascertained in view of one skilled in the art. "It is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations" *(Martin v. Mayer,* 823 F.2d 500, 3 USPQ 2d 1333 [Fed. Cir. 1987]).

Furthermore, it is not necessary to provide the amino acid sequence in the specification where the sequence is known in the art. The United States Court of Appeal for the Federal Circuit held in *Capon v. Eshar* that:

> *The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specification do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.*

Multiple Fusion Molecules are Described in the Specification

The Examiner alleges that the Specification discloses insufficient written description of the structure of fusion molecules of the claimed invention to support a claim to a larger genus of fusion molecules.

Applicant must respectfully disagree. As described above, the Specification describes multiple fusion molecules. For example, the Specification describes the construction of chimeric fusion molecules, see Example 2, pages 180-183. The Specification also describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 21, line 4 - 24). The Specification describes advantageous fusion molecule variants (page 21, line line 25 - page 23, line 3), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 34, line 24 - page 35, line 25). The Specification describes fusion molecules comprising multiple copies of IgG and autoantigen (page 54, lines 18-21). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 63, line 32 to page 64, line 3) are also described.

In view of the fusion molecules described above and the level of skill in the art, Applicant asserts that sufficient representative fusion molecules are adequately described in the Specification (without undue detail) to support a genus of fusion molecules, as recited in Claim 1, and all claims dependent on Claim 1. Applicant respectfully requests withdrawal of this rejection.

The Examiner alleges that the Specification fails to provide sufficient written description of polypeptides having at least 85% sequence identity with the IgG constant domain sequences *(e.g.,* 85% sequence identity with SEQ ID NO: 3) where the molecules retain biological activity.

Applicant respectfully traverses the rejection. Applicant points out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4 - 13). Also, the Specification provides examples of prior art that describes numerous Ig Fc polypeptides having at least 85% sequence identity with the Fc sequences of SEQ ID NO: 3 *(see,* the Specification at page 26, line 19 to page 27, line 6). The Specification also describes

methods for the identification of Ig Fc sequences having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 (see the Specification at page 23, line 16 to page 24, line 12). Alternatively still, one of ordinary skill in the art can readily engineer novel Fc domains having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using recombinant DNA/protein engineering techniques.

With respect to the second polypeptide, the sequence for MBP was known in the art prior to Applicant's filing. Applicant provides a number of references in the specification at page 46 which provide the sequence for MBP, see for example, Warren et al., Proc. Natl. Acad. Sci. USA 92:11061-65 (1995). The specification identifies the MBP epitope necessary for binding with the autoantibody as MBP83-99. Clearly Applicant had possession of the invention at the time of filing.

Applicant points out that all pending claims reciting polypeptides having at least 85% sequence identity with IgG Fc domains *(e.g.,* having 85% sequence identity with SEQ ID NOs: 3) contain the functional limitation that the polypeptides also have the ability to bind to the IgG cell surface receptor. The Specification provides description of this limitation where the amino acids necessary for receptor binding and biological activity (page 35, lines 1-25) and methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15 - 25) are described.

Applicant argues that the Specification provides adequate written description for fusion molecules comprising polypeptides having at least 85% sequence identity with IgG constant domain sequences *(e.g.,* 85% sequence identity with SEQ ID NO: 3), especially in view of the state of the prior art, and the high level of skill in the art. Applicant further argues that the scope of the claims finds written description throughout the Specification, and are allowable. The Examiner is respectfully requested to withdraw this rejection.

5. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,420, 247 in view of Warren et al. (PNAS 1995) and Tisch et al., (J. Immunology Feb. 2001)

Claims 1, 4-6, 9-14, 16, 22-28 and 40-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,420,247 in view of Warren et al. (Proc. Natl. Acad. Sci. USA 92: 11061-65 (1995)) and further in view of Tisch et al., (J. Immunology Feb. 2001). It allegedly would have been obvious to substitute the LIF-R in the fusion molecule as taught by the '247 patent for the autoantigen such as myelin basic protein (MBP) as taught by Warren et al. for a fusion molecule comprising a first polypeptide IgG heavy chain constant region connected to myelin basic protein through a polypeptide linker as taught by the '247 patent and Warren et al. Alternatively it allegedly would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute the autoantigen GA65 in the fusion molecule as taught by Tisch et al., for the myelin basic protein as taught by Warren et al. From the combined teachings of the references, it is allegedly apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor

The '247 patent teaches LIF-R proteins. The '247 patent teaches that the LIF-R peptide may be fused to an antibody Fc region, which comprises the hinge region in order to allow dimerization of the peptide chains through binding of the cysteine residues in the hinge region. The '247 patent does not teach or suggest a fusion molecule of the IgG heavy chain constant region fused to an MBP peptide.

Warren et al., teach autoantigen sequences such as myelin basic protein and various antigenic epitopes or fragments thereof such as MBP84-93. Warren et al.

teach that free and/or cerebrospinal fluid tissue bound autoantibodies to MBP are found in a large number of patients with MS and optic neuritis. Increased anti-MBP levels are highly associated with disease activity. Warren does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. Warren does not teach or suggest the administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease.

TIsch et al. teaches that intramuscular injection of plasmid DNA encoding GAD65-IgGFc and IL-4 prevented diabetes in NOD mice treated at early or late preclinical stages of IDDM. Tisch teaches that in an attempt to efficiently stimulate CD4+ T cells, the GAD65 specific DNA sequence was fused to a human IgG4Fc DNA molecule. In this way, the fusion protein is secreted and the GAD65 specific epitopes should be preferentially processed and presented via the MHC class II pathway. Tisch teaches that the pDNA efficacy diminishes with time. Tisch teaches that progression of overt IDDM can be suppressed in NOD mice at late preclinical stages of disease by IV or IP injection of soluble GAD65 specific peptides prepared in the appropriate adjuvant. However, multiple immunizations with relatively high doses of peptide are necessary to effectively induce regulatory Th2 cells. Tisch et al. does not teach or suggest the administration of the GAD65-FcIgG fusion protein to animals. Tisch does not teach or suggest the use of MBP peptides for the treatment or prevention of autoimmune disease. Tisch et al. indicates that the pDNA is administered for presentation in the MHC pathway and that the "immune deviation was dependent upon pDNA-encoding IL-4". Tisch does not teach using the FcIgG coupling so as to prevent established allergic (IgE reactivity) in sensitized or even immune animals.

In view of the deficiencies in the cited references as described above, the claimed invention is not obvious under 35 U.S.C. § 103 for the following reasons.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and (2) whether the prior art would also have revealed

that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck* 947 F 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. While the '247 patent teaches LIF-R fused with IgG, the purpose of adding IgG was to generate a dimer molecule. While the Warren et al. reference teaches MBP peptides there is no teaching or suggestion to combine the peptide with an IgG Fc region. While Tisch et al teaches the administration of a pDNA encoding the GAD65 DNA sequence fused to a human IgG4 Fc sequence, the pDNA is administered to the animal and the purpose is to increase the MHC presentation of the GAD65 sequences which are known to suppress IDDM. There is no teaching to administer a fusion peptide, let alone a peptide comprising the MBP peptide.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '247 patent uses the IgG heavy chain region to generate a dimer molecule to obtain the biologic function of the LIF molecule. It provides no motivation to replace the LIF-R4 peptide with an MBP peptide in which the MBP serves as an immunogen/tolergen. There is no motivation in Warren et al. to attach the MBP peptide to an IgG heavy region. There is no motivation to generate a fusion protein comprising the MBP peptide. The Tisch et al. reference teaches the use of pDNA. It does not teach the administration of a peptide. The Tisch reference provides no motivation to replace the GAD65 DNA sequence with an MBP DNA sequence and then administer the fusion peptide. There is no motivation to generate a fusion protein comprising the MBP peptide.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is <u>not</u> obvious. Thus, withdrawal of this rejection is respectfully requested.

6. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,420,247 in view of Warren et al., and Tisch et al., and further in view of U.S. Patent 5,565,335

Claims 1-4, 15 and 18-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,420,247 in view of Warren and Tisch and further in view of U.S. Patent 5,565,335. The Office Action states that it would have been obvious to one having ordinary skill in the art at the time to substitute the Fc polypeptide in the fusion protein as taught by the '247 patent or the FcIgG4 in the fusion molecule as taught by Tisch et al., for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO:3 as taught by the '335 patent for a fusion molecule comprising a human IgG Fc constant region functionally connected to any second autoantigen polypeptide sequence such as MBP as taught by Warren et al., the '247 patent , Tischet al. and the 335 patent. One would allegedly have been motivated because the '247 patent teaches the IgG Fc fusion molecule can be easily purified. Tisch et al. teach the autoantigen specific sequence when human IgG4Fc is secreted and the autoantigen specific epitope would be processed via the MHC class II pathway. The '335 patent allegedly teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule.

The Examiner states that Applicant's arguments have been considered but are not found persuasive. Applicant notes that this is a new rejection combining new references for which some references have not previously been cited. Applicant has not made previous arguments to this specific combination of references.

Claim 1 recites an isolated fusion molecule comprising a polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor.

U.S. Patent 5,420,247, Warren et al., and Tisch et al., have been discussed above.

U.S. Patent No. 5,565,335 teaches soluble secreted adhesons comprising the CD4 protein. The CD4 adheson ordinarily binds to the recognition sites of HIV and the purpose of the patent is to design candidates for therapeutically sequestering these HIV sites, thereby blocking viral infectivity. The '335 patent teaches fusing the CD4 polypeptide with a protein with a long plasma life such as an immunoglobulin constant domain. The purpose of this fusion is to increase the half-life of the CD4 polypeptide. The '335 patent teaches the CD4 peptide linked to the IgG1 heavy chain constant region. The '335 patent teaches that adhesons are cell surface polypeptides having an extra-cellular domain which is homologous to a member of the immunoglobulin gene superfamily, excluding however, highly polymorphic members of the superfamily. (Col. 4, lines 7 - 14). The patent lists a number of examples of adhesions. Myelin basic protein is not an adheson. There is no teaching or suggestion of autoantigens. There is no teaching or suggestion in the '335 patent to replace the CD4 molecule in the immunoadheson with an MBP peptide. Such a replacement would be against the purpose of the '335 patent.

The claimed invention is not obvious under 35 U.S.C. § 103 in light of the references for, at least, the following reasons.

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. While the '247 patent teaches LIF-R fused with IgG, the purpose of adding IgG was to generate a dimer molecule. While the Warren reference teaches the MBP peptide, there is not teaching to combine it with the IgG Fc. While the Tisch et al reference teaches combining the GAD65 peptide with the IgG4 Fc, there is no teaching of combining the MBP peptide with IgG Fc. While the '335 patent teaches CD4 fused with IgG there is no teaching or suggestion to combine an MBP peptide with an IgG Fc region.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '247 patent uses the IgG heavy chain region to generate a dimer molecule to obtain the biologic function of the LIF molecule. It provides no motivation to replace the LIF-R4 peptide with an MBP peptide.

The '335 patent teaches CD4 fused with IgG. There is no motivation in the '335 patent to replace the CD4 with an MBP peptide.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is not obvious. Thus, withdrawal of this rejection is respectfully requested.

7. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,420, 247 in view of Warren et al., and Tisch et al., and further in view of Elias et al. and Marks et al.

Claims 1, 27 and 29-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,420,247 in view of Warren et al., and Tisch et al., and further in view of Elias et al., (J. Biol. Chem 265(26) 15511-17, (1990) and Marks et al., (J. Cell Biol. 135(2) 341-354, (1996). The Office Action states that it would have been obvious to add at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule as taught by the '247 patent to target the transmembrane protein such as IgFc connected to LIF-R through a peptide linker to route the fusion molecule to the lysosome and endosome antigen processing as well as modulating the half-life of the fusion molecule as taught by the '247 patent, Elias et al. and Marks et al.

This rejection is traversed for the following reasons.

The claimed invention is not obvious in light of the combination of the cited references for the following reasons.

The '247 patent, Warren et al., and Tisch et al., have been discussed above.

Elias et al. teach N terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase to conjugated protein to ubiquitin for protein degradation. Elias et al. teach hydrophobic amino acid residues such as leucine or basic amino acid residues such as histidine, arginine and lysine determine the half-life of the protein.

Mark et al. teach that adding ubiquitination target motifs such as bulky hydrophobic group di-leucine motifs to any protein would target the protein to the lysosome or endosomal compartments for antigen processing.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck* 947 F 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. The '247 patent, Warren et al. and Tisch et al. do not teach or suggest the fusion of a heavy constant region of the IgG molecule with a myelin basic peptide fragment. The Elias and Marks references do not cure this deficiency.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '247 patent uses the IgG heavy chain region to generate a dimer molecule. It provides no motivation to replace the LIF-R4 peptide with an MBP peptide. The Elias and Marks references do not cure this deficiency.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is not obvious. Thus, withdrawal of this rejection is respectfully requested.

8. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 5,420, 247 in view of Warren et al., and Tisch et al., and further in view of U.S. Patent No. 5,945,294

Claims 1, 9 and 42-44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,420,247 in view of Warren et al. and Tisch et al.

and further in view of U.S. Patent No. 5,945,294. The Office Action states that it allegedly would have been obvious to substitute the human Fc epsilon receptor as taught by the '294 patent for the fusion protein as taught by the '247 patent, Warren et al., and Tisch et al., in the kit for diagnostic assays.

Claim 1 recites an isolated fusion molecule comprising a first polypeptide sequence having at least 85% identity with an IgG heavy chain constant region sequence capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of basic myelin protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor.

The '247 patent, Warren et al., and Tisch et al., have been discussed above.

The '294 patent teaches diagnostic kits for IgE detection comprising human Fc epsilon receptor and an allergen.

Claims 1 and 9 are not directed to a kit. Thus, withdrawal of the rejection regarding these claims is requested.

Neither the "247, nor Warren et al., nor Tisch et al., nor the '294 patent nor a combination of both teaches or suggests the fusion protein of the IgG Fc region with the MBP peptide in a kit. Absent such a teaching or suggestion, the invention is not obvious within the meaning of 35 U.S.C. § 103.

Thus, withdrawal of this rejection is respectfully requested.

Applicant notes with appreciation that Claim 17 is free of the prior art.

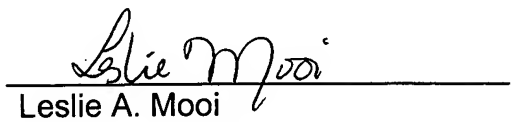
9. Conclusion

Applicant believes that this application is in condition for allowance.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 20, 2005



Leslie A. Mooi
Reg. No. 37,047

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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IN THE FIGURES

Applicant encloses a replacement Figure 9.